REMARKS

Applicants respectfully request reconsideration of the present application in view of the foregoing amendments and the following remarks.

I. Status of the Claims

With this submission, no claims are amended, canceled or newly added. Thus, upon entry of this paper, claims 1-23, 25 and 29-30 are currently pending and under active consideration.

A detailed listing of all claims that are, or were, in the application, irrespective of whether the claims remain under examination in the application, is presented, with an appropriate defined status identifier.

II. Claim Rejection Under 35 U.S.C. § 103(a)- Abramson in view of Lee

The Office Action, at pages 5-12, rejects claims 1-13, 15, 20-22 and 30 under 35 U.S.C. § 103(a) as allegedly being obvious over Abramson (US 2003/0077572), in view of Lee (US Patent Application Publication No. 2003/0180710). Applicants respectfully traverse this ground of rejection.

A. Embodiments of the Invention

Embodiments of the claimed invention are directed to methods for analyzing the metabolites of a biological sample, which comprises quantitatively determining one or more metabolites in the sample in a way that the quantitative determination resolves isotopic mass differences within one metabolite, wherein the sample comprises or is derived from a cell which has been maintained under conditions which allow the uptake of an isotopically-labeled metabolizable compound so that the metabolites in the cell are saturated with the isotope with which the metabolizable compound is labeled.

B. A Skilled Artisan Could Not Combine Abramson with Lee

The Office bases its arguments on an erroneous assumption. Specifically, the Office argues that "[t]he method of analysis taught by Abramson, CRIMS, may be substituted by the

method of Lee comprising chromatography interfaced with a mass spectrometry for ratio analysis of isotopomers" (Office Action, page 4).

The Examiner is reminded that "[i]f proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification. *In re Gordon*, 733 F.2d 900, 211 USPQ 1125 (Fed. Cir. 1984)." MPEP 2143.01 Section V.

As previously noted in the declaration by Dr. Willmitzer (Declaration filed May 27, 2010), one of skill in the art would not combine Abramson and Lee. In contrast to the claimed invention, **Lee would not be operable if he used uniformly and saturated labelled samples**. Lee only discloses a method of determining dynamics (time dependant distribution) and pathways (specifically labelled compounds and position of labelling within a compound). If Lee were to use uniformly and saturated labelled samples, Lee could not determine the dynamics or pathways involved (Willmitzer Declaration, paragraph 8), thereby frustrating the very purpose of Lee's invention.

Additionally, Lee's use of mass spectrometry for isotope dilution analysis **does not have the intention or function of absolute quantifiation** and **does not use the combination of samples** for this purpose. As discussed above, Lee's method and objective is clearly **contrary** to the challenge of the claimed invention that it could not and would not be taken into account for solving the problem in combination with the disclosure of Abramson. Accordingly, one of skill in the art would not look to Lee to solve the clear deficiencies found in Abramson's CRIMS methodology.

C. Abramson and/or Lee Do Not Teach the Claimed Invention

The combination of Lee's method with Abramson's disclosure would not make the finding obvious to a person skilled in the art. Abramson discloses differential labeling of two cell populations, each labeled to a different extent. Thus, Abramson fails to teach or suggest the claimed invention.

As previously noted, Abramson teaches the saturated, uniform labelling of a sample and the combination with an unlabelled, but treated, sample for quantification purpose.

(Willmitzer Declaration, paragraph 10) Therefore, Abramson does not teach a method for analysing the metabolites of a biological sample which comprises quantitatively determining one or more metabolites in said sample in a way that said quantitative analysis resolves isotopic mass differences within one metabolite. (Willmitzer Declaration, paragraph 10) Specifically, Abramson only measures the isotopic mass difference of the combustion products but not the metabolites. (Willmitzer Declaration, paragraph 10) This type of analysis is a convenient, simple and easy way to apply isotope dilution analysis, however, the output contains only **two-dimensional data**. (Willmitzer Declaration, paragraph 12)

Abramson is based on the **combustion** process necessary to decompose the sample. (Willmitzer Declaration, paragraph 13) Specifically, all structural information of the metabolites is lost because the sample is decomposed via combustion. (Willmitzer Declaration, paragraph 13) As such, Abramson characterizes metabolites using only chromatographic retention time. (Willmitzer Declaration, paragraph 13) Thus, **two dimensional** chromatography, as described in Abramson, is **insufficient for calculating individual quantitative results on thousands of compounds**. (Willmitzer Declaration, paragraph 14) Therefore, Abramson is not suited for complex metabolomic analysis. (Willmitzer Declaration, paragraph 14)

Applicants have added a **third dimension** of analysis not present in either Abramson or Lee. Specifically, this third dimension consists of analysis of the molecular and fragment ions masses. The third dimension increases the selectivity in a manner so that completely coeluting compounds with known and different mass spectra can easily be resolved. Surprisingly, even partly coeluting metabolites with unknown mass spectra can be resolved by deconvolution. (Willmitzer Declaration, paragraph 16) This is a crucial improvement for metabolomics because never before could one of skill in the art analyze a high number of compounds. Specifically, the quantification quality of previous methods are limited because the high number of compounds were poorly resolved when using only chromatography (Abramson).

In sum, Abramson does not teach a method for analysing the metabolites of a biological sample which comprises quantitatively determining one or more metabolites in

said sample in a way that said quantitative analysis resolves isotopic mass differences within one metabolite. Specifically, Abramson only measures the isotopic mass difference of the combustion products but not the metabolites.

For at least these reasons, Applicants respectfully request reconsideration and withdrawal of the rejection.

III. Claim Rejection Under 35 U.S.C. § 103(a)- Abramson in view of Lee and Kasper

The Office rejects claim 14 under 35 U.S.C. § 103(a) as allegedly being obvious over Abramson in view of Lee and Kasper (US Patent Application Publication No. 2005/0112706). Applicants respectfully traverse this ground of rejection.

Kasper discloses methods for determining androgen responsiveness in a sample using bioassays. Kasper fails to teach or suggest cell labeling, let alone saturated labeling. Thus, Kasper fails to remedy the deficiencies of Abramson and/or Lee.

Accordingly, the rejection is improper and should be withdrawn.

IV. Claim Rejection Under 35 U.S.C. § 103(a)- Abramson in view of Lee and Birkemeyer

The Office rejects claim 14 and 15 under 35 U.S.C. § 103(a) as allegedly being obvious over Abramson in view of Lee and Birkemeyer (J. Chromatography A 993: 89). Applicants respectfully traverse this ground of rejection.

Birkemeyer discloses gas chromatography analysis of phytohormones. The reference fails to teach or suggest isotope labeling, let alone saturated labeling, and thus fails to remedy the deficiencies of Lee described above.

Thus, the rejection is improper. Reconsideration and withdrawal of this ground of rejection are therefore respectfully requested.

V. Claim Rejection Under 35 U.S.C. § 103(a)- Abramson in view of Lee and Hellerstein-APEM

The Office rejects claims 18-19 under 35 U.S.C. § 103(a) as allegedly being obvious over Abramson in view of Lee and MK Hellerstein and RA Neese 1999 *American J. Physiol. Endocr. Metab.* 276: 1146- 1170 ("Hellerstein-APEM"). Applicants respectfully traverse this ground of rejection.

Hellerstein-APEM fails to remedy the deficiencies of Abramson and Lee described above, as the reference provides a review of mass isotopomer distribution. Accordingly, the rejection is improper and should be withdrawn.

VI. Claim Rejection Under 35 U.S.C. § 103(a)- Abramson in view of Lee and Hellerstein

The Office rejects claim 25 under 35 U.S.C. § 103(a) as allegedly being obvious over Abramson and Lee in view of US Patent Application Publication No. 2004/00811994 A1 to Hellerstein ("Hellerstein"). Applicants respectfully traverse this ground of rejection.

Hellerstein discloses biochemical methods for assessing metabolic fitness. The reference fails to teach or suggest cell labeling, and thus fails to remedy the deficiencies of Lee described above. Accordingly, the rejection is improper and should be withdrawn.

VII. Claim Rejection Under 35 U.S.C. § 103(a)- Lee in view of Abramson and Evans

The Office rejects claim 23 under 35 U.S.C. § 103(a) as allegedly being obvious over Lee in view of Abramson and US Patent No. 5,532,206 to Evans *et al.* ("Evans"). Applicants respectfully traverse this ground of rejection.

Evans does not remedy the deficiencies of Lee described above as the patent discloses application of C-16,17- dihydro gibberellin to plants.

Accordingly, the rejection is improper and should be withdrawn.

VIII. Claim Rejection Under 35 U.S.C. § 103(a)- Lee in view of Abramson and Evans and Hellerstein- '994

The Office rejects claim 29 under 35 U.S.C. § 103(a) as allegedly being obvious over Lee in view of Abramson, and Evans and further in view of US Patent Application Publication No. 2004/00811994 A1 to Hellerstein ("Hellerstein"). Applicants respectfully traverse this ground of rejection.

The reference fails to teach or suggest cell labeling, and thus fails to remedy the deficiencies of Lee, Abramson, and/or Evans as described above. Accordingly, the rejection is improper and should be withdrawn.

CONCLUSION

All of the stated grounds of objection and rejection have been properly traversed or rendered moot. Thus, the present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested.

The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by a check being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing or a credit card payment form being unsigned, providing incorrect information resulting in a rejected credit card transaction, or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicants hereby petition for such extension under 37 C.F.R. § 1.136 and authorize payment of any such extensions fees to Deposit Account No. 19-0741.

Respectfully submitted,

By _____

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